REMARKS

In the Office Action dated April 11, 2008, claims 1-17 and 22-71 were rejected. The Examiner made the rejection final. In response, Applicant has submitted a Request for Continued Examination (RCE) together with a request for a one-month extension of time. Reconsideration of this application is requested in view of the following remarks.

In the Office Action, claims 1-17 and 22-71 stand rejected under the judicially-created doctrine of obviousness type double patenting as being unpatentable over the claims of U.S. Patent Nos. 5,843,928; 6,392,071; 6,440,953; 6,482,812; 6,537,981; 6,696,431; 6,774,251; 6,806,262; 6,894,037; 6,992,074; 7,053,075; 7,115,594; 7,208,484; 7,214,670; 6,214,671; 7,232,810; 7,241,747; 7,241,909 and 7,244,719 in view of Bishop et al U.S. 5,972,917 or DeLuca et al WO 96/16035. The Examiner contends that each of these patents teaches 2-alkylidene-19-nor vitamin D compounds useful in treating various diseases such as osteoporosis. Although the Examiner recognizes that the instantly claimed compounds differ from the 2-alkylidene-19-nor vitamin D compounds of the prior art as being 18, 19-dinor derivatives thereof, the Examiner believes that said compounds are rendered obvious, and states:

> "Applicant argues the references do not teach an equivalent in biological activity with hydrogen and methyl at the 18-position. The issue is whether the 18-nor compounds of 5,**843,928; 6,392,071; 6,440,953; 6,482,812; 6,537,981; 6,696,431; 6,774,251; 6,806,262; 6,894,037; 6,992,074; 7,053,075; 7,115,594; 7,208,484; 7,214,670; 6,214,671; 7,232,810; 7,241,747; 7,241,909 and 7,244,719** would have been obvious to the skilled artisan based on the teachings of the prior art and the level of skill of the ordinary artisan in the art at the time of the present invention. As discussed in the previous Office Action, the prior art teaches both 18-methyl and 18-nor vitamin D compounds are useful in treating similar diseases such as psoriasis, osteoporosis, multiple sclerosis, etc. (see Delua and Bishop). Therefore, the 18-nor compounds of **5,843,928; 6,392,071; 6,440,953; 6,482,812; 6,537,981; 6,696,431; 6,774,251; 6,806,262; 6,894,037; 6,992,074; 7,053,075; 7,115,594; 7,208,484; 7,214,670; 6,214,671; 7,232,810; 7,241,747; 7,241,909 and 7,244,719** are rendered obvious because the skilled artisan would have the reasonable expectation that said compounds would also be useful in treating diseases such as psoriasis, osteoporosis, multiple sclerosis, etc.

> Additionally, as shown by both references, i.e., Bishop and DeLuca, and argued by applicant, the ability of vitamin D compounds to affect calcium transport and cell differentiation changes with the presence of hydrogen and/or methyl at the 18-position. As taught by DeLuca, the skilled artisan would have the reasonable expectation that the corresponding 18,19-nor compounds of **5,843,928; 6,392,071; 6,440,953; 6,482,812; 6,537,981; 6,696,431; 6,774,251; 6,806,262; 6,894,037; 6,992,074; 7,053,075; 7,115,594; 7,208,484; 7,214,670; 6,214,671; 7,232,810; 7,241,747; 7,241,909 and 7,244,719** would be useful as known in the art for vitamin D compounds but would be characterized by high cell differentiation activity and marked intestinal calcium transport activity as taught by DeLuca."

The Applicant disagrees that the presently-claimed compounds are rendered obvious in view of the cited patents for the following reasons.

The Examiner believes the instantly claimed 18,19-dinor vitamin D compounds are rendered obvious because a person skilled in the art would have a reasonable expectation that the presently-claimed 18,19-dinor compounds would also be useful in treating diseases such as osteoporosis. By the following argument, Applicant will demonstrate to the Examiner that the biological activities of vitamin D compounds are unpredictable, and thus one skilled in the art will not be able to predict with any certainty the activity of any particular vitamin D compound until such vitamin D compound is actually tested for such activities. As such, one skilled in the art could not predict with any reasonable expectation of success that a particular 18,19-dinor compound would be useful to treat a disease such as osteoporosis, as the Examiner alleges.

First, Applicant would like to cite the following quotation from Published PCT International Application No. WO 93/19044 at page 5, lines 25-36 thereof:

> "The fact that there are only small structural differences between the compounds of the prior art referred to above indicates that the present state of knowledge does not allow prediction of the structure of vitamin D analogues which will show a favourable degree of selectivity, as reflected by a higher cell differentiating activity in vitro compared to the binding affinity for intestinal vitamin D receptor in vitro. Furthermore, the matter is complicated by the observation that receptor binding affinities in vitro are not always paralleled by in vivo studies, probably reflecting a pharmacokinetic difference between the compounds."

The Examiner should note that the above quotation is not made by any of the inventors of the present patent application. The inventors of WO 93/19044 are independent of the present Applicant and/or inventors and provides a completely unbiased opinion. Thus, the Examiner should note that it is recognized by those skilled in this art that the biological activities of vitamin D analogs are not predictable, and one cannot assume that the same structural change between different analogs will result in the same biological activities.

In order to demonstrate to the Examiner that the activity of the corresponding 18-nor vitamin D analog is unpredictable as compared to the structurally similar parent compound having a methyl group at the 18 position, Applicant will hereinafter compare the biological activities of three different groups of vitamin D compounds. The first comparison is between 1α,25-dihydroxyvitamin D_3 and 18-nor-1α,25-dihydroxyvitamin D_3. The second comparison involves 19-nor-1α,25-dihydroxyvitamin D_3 versus 18,19-dinor-1α,25-dihydroxyvitamin D_3. The final comparison involves 1α-hydroxy-2-methylene-19-nor-homopregnacalciferol versus 1α-hydroxy-2-methylene-18,19-dinor-homopregnacalciferol.

The biological activities of 1α,25-dihydroxyvitamin D_3 and 18-nor-1α,25-dihydroxyvitamin D_3 are described in related U.S. Patent Nos. 5,661,140; 5,767,110 and 5,721,224. Looking at the '224 patent, the Examiner will see that a comparison of the bone calcium mobilization activity of 1α,25-dihydroxyvitamin D_3 and 18-nor-1α,25-dihydroxyvitamin D_3 is set forth in Table 2 at column 16 thereof. In describing the significance of the data, it is stated at column 16, lines 57-60 that:

> "Table 2 shows that 18-nor-1α,25-dihydroxyvitamin D_3, while having similar ability to mobilize calcium from bone, is clearly not as active in this regard as 1α,25-dihydroxyvitamin D_3."

As a result, the '224 patent concludes that the 18-nor-1α,25-dihydroxyvitamin D_3 analog has "relatively low ability to mobilize calcium from bone." Nevertheless, it is stated in the '224 patent that the 18-nor analog may be useful "for the treatment of metabolic bone diseases where bone loss is a major concern such as osteoporosis, osteomalacia and renal osteodystrophy." See column 16, line 66 through column 17, line 2. However, because the 18-nor compound has some ability to mobilize calcium from bone, albeit significantly less

than 1α,25-dihydroxyvitamin D_3, it is opined that it may be useful to treat metabolic bone diseases depending upon the disease being treated, the condition of the patient, and other relevant medical facts, as is well-known in the art.

The biological activities of 19-nor-1α,25-dihydroxyvitamin D_3 versus 18,19-dinor-1α,25-dihydroxyvitamin D_3 are given in WO 96/16035 which is cited by the Examiner in the present Office Action. The calcemic activity of these compounds is given in Table 1 at page 27 thereof. WO 96/16035 concludes that:

> "Table 1 shows that 18,19-dinor-1α,25-dihydroxyvitamin D_3, while having similar ability to mobilize calcium from bone, is clearly not as active in this regard as 1α,25-dihydroxyvitamin D_3. Also, Table 1 shows that 18,19-dinor-1α,25-dihydroxyvitamin D_3 is almost as active as 1α,25-dihydroxyvitamin D_3 in intestinal calcium transport activity.
>
> Thus, the 18,19-dinor analog shows a selective activity profile combining high potency in inducing the differentiation of malignant cells, relatively high intestinal calcium transport activity with relatively low bone calcium mobilization activity. The compounds of this novel structural class, therefore, can be useful as therapeutic agents for the treatment of psoriasis and other malignancies, and for the treatment of metabolic bone diseases where bone loss is a major concern such as osteoporosis, osteomalacia and renal osteodystrophy."

Thus, WO 96/16035 concludes that the 18,19-dinor analog taught therein may be useful to treat osteoporosis, even though it has different calcemic activities than the corresponding parent analog 19-nor-1α,25-dihydroxyvitamin D_3. Again, however, it is opined that the 18,19-dinor compound may be useful to treat metabolic bone diseases depending upon the relevant medical facts of a patient's condition even though it has "relatively low" bone calcium mobilization activity.

Thus, it might be concluded that in the above two examples the 18-nor analog might be useful to treat metabolic bone diseases such as osteoporosis. However, that is not true for all 18-nor vitamin D compounds, as the Applicant will now demonstrate.

The Examiner cites U.S. 6,440,953 as an example of a 2-methylene-19-nor compound in which the corresponding 18-nor compound would be expected to be useful in treating diseases such as osteoporosis. However, the data published in connection with the

corresponding 18-nor analog thereof demonstrates otherwise. More specifically, Applicant refers the Examiner to U.S. Patent No. 7,238,681 which teaches the corresponding 18,19-dinor analog of the 2-methylene analog disclosed in U.S. 6,440,953 cited by the Examiner. The biological activity of the 18-nor compound disclosed in '681 is set forth in Figures 4 and 5, and discussed at column 13, line 53 through column 14, line 2 as follows:

> "FIG. 4 shows that 18,19-dinor-2MP has little, if any, activity in mobilizing calcium from bone, and its activity is about equivalent to 2MP. Administration of 18,19-dinor-2MP at 780 pmol/day for 4 consecutive days did not result in mobilization of bone calcium, and increasing the amount of 18,19-dinor-2MP to 2340 pmol/day or to 7020 pmol/day was also without any substantial effect.
>
> Intestinal calcium transport was evaluated in the same groups of animals using the everted gut sac method (FIG. 5). These results show that the compound 18,19-dinor-2MP does not promote intestinal calcium transport when administered at 780 pmol/day, 2340 pmol/day or 7020 pmol/day, whereas $1,25(OH)_2D_3$ promotes a significant increase at the 780 pmol/day dose, and 2MP also provides a significant increase at a 2340 pmol/day dose. Thus, it may be concluded that 18,19-dinor-2MP is essentially devoid of intestinal calcium transport activity at the tested doses."

As the Examiner can see, the corresponding 18-nor compound has little, if any, calcemic activity. As a result, this compound would not be useful in treating metabolic bone diseases such as osteoporosis, osteomalacia and/or renal osteodystrophy. The Examiner will specifically note that in the '681 patent no mention is made of this compound's usefulness in treating metabolic bone diseases. The obvious reason is that it has no calcemic activity.

Thus, the 18-nor compound disclosed in U.S. 7,238,681, although being an 18-nor compound, would not be useful in treating metabolic bone diseases. If, as alleged by the Examiner, one skilled in the art would have assumed that the 18-nor analog disclosed in the '681 reference would have been useful to treat metabolic bone diseases, that person skilled in the art would be wrong.

In summary, one skilled in the art cannot predict the biological activities of corresponding 18-nor compounds. As such, one skilled in the art would not have a reasonable expectation of success alleged by the Examiner. Withdrawal of the obviousness

type double patenting rejection based on Bishop et al '917 and/or DeLuca et al '035 is herein requested.

In the Office Action, claims 1-17 and 22-71 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over the claims of co-pending application nos. 10/997,698 and 11/351,874 in view of Bishop et al U.S. 5,972,917 or DeLuca et al WO 96/16035.

In response, Applicants traverse the rejection for the same reasons as noted above. For those reasons, one skilled in the art would not recognize that hydrogen and methyl are equivalent at the carbon 18 position for all vitamin D compounds. Therefore, the presently claimed compounds having 18-nor as well as 19-nor and 2-alkylidene modifications should not be rejected under the doctrine of obviousness type double patenting over the compounds claimed in the cited applications, which do not include 18-nor modifications. Reconsideration and withdrawal of this rejection is herein requested.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

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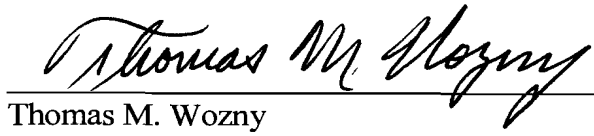

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